Award Number:

W81XWH-10-1-0582

TITLE:

ETS Gene Fusions as Predictive Biomarkers of Resistance to Radiation Therapy for Prostate Cancer

PRINCIPAL INVESTIGATOR:

Felix Feng, M.D.

CONTRACTING ORGANIZATION:

Regents of the University of Michigan
Ann Arbor, MI 48109

REPORT DATE:

October 2015

TYPE OF REPORT:

Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE	**2. REPORT TYPE**	**3. DATES COVERED**
October 2015	Annual Summary	15 JUL 2010 - 14 JUL 2015

4. TITLE AND SUBTITLE

ETS Gene Fusions as Predictive Biomarkers of Resistance to Radiation Therapy for Prostate Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-0582

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Felix Feng, M.D.

E-Mail: ffeng@med.umich.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Michigan
503 Thompson St
Ann Arbor, MI 48109-1340

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The research goals of this grant proposal are to: 1) investigate the effect of ETS gene fusions on radiation phenotype in preclinical models of prostate cancer, 2) to explore the mechanism of interaction between ERG (the predominant ETS gene fusion product) and the DNA repair protein DNA-PK, and 3) to determine if ETS gene fusion status is a clinical biomarker of radioresistance for prostate cancer. The training goals of this grant proposal included a series of regular meetings with mentors, research seminars, journal clubs, and workshops, all of which are intended to help Dr. Feng develop as a translational scientist. This grant proposal was approved as a five-year award; the current annual report summarizes accomplishments over the fifth year of the grant, from July 15, 2014 to July 15, 2015.

Overall, this grant effort has been very successful. The work accomplished as a result of this grant resulted in seven publications in very high-impact journals, five presentations, and five grants (three from the Prostate Cancer Foundation, one from Celgene, and one from the Fund for Cancer Research). Additionally, Dr. Feng has met the training achievements specified in his original grant.

The research proposed in this training grant represents an important area within the field of prostate cancer research. Because ETS gene fusions are thought to be driver alterations in over half of all prostate cancers, understanding the mechanistic and potential clinical implications of these gene fusions has significant ramifications, particularly in the context of radiation therapy, which represents a primary treatment modality for localized prostate cancer. In the fifth year of this grant period, we have accomplished another two subtasks, for a total of 19 out of 20 originally proposed subtasks. We are requesting a no-cost extension to allow us to accomplish the final and 20th subtask. Our work has helped define the functional significance of the interaction between ETS gene fusions and DNAPK inhibition, and has established this axis as a potential therapeutic target. In total, our findings suggest that DNA-PK inhibition should be explored as a clinical strategy for radiosensitizing prostate cancers.

15. SUBJECT TERMS Prostate cancer, ETS gene fusions, ERG, radiation resistance, DNA-PK					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U	UU	13	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

	Page
Introduction……..…….	**5**
Body…….	**5**
Key Research Accomplishments…….…….	**11**
Reportable Outcomes……	**11**
Conclusion……	**12**
References……	**13**
Appendices……	**13**

Introduction

This annual report will summarize the accomplishments associated with the Department of Defense Physician Research Training Award (W81XWH-10-1-0582), awarded to Felix Feng, M.D. This award included both research goals and training goals. The research goals of this grant proposal are to: 1) investigate the effect of ETS gene fusions on radiation phenotype in preclinical models of prostate cancer, 2) to explore the mechanism of interaction between ERG (the predominant ETS gene fusion product) and the DNA repair protein DNA-PK, and 3) to determine if ETS gene fusion status is a clinical biomarker of radioresistance for prostate cancer. The training goals of this grant proposal included a series of regular meetings with mentors, research seminars, journal clubs, and workshops, all of which are intended to help Dr. Feng develop as a translational scientist, with the ultimate goals of submitting a NIH-level grant as an independent investigator and developing a translational clinical trial. This grant proposal was approved as a five-year award; the current annual report summarizes accomplishments over the fourth year of the grant, from July 15, 2014 to July 15, 2015.

Body

Research achievements: Tasks and Subtasks

As outlined in the original Statement of Work, this grant proposal was comprised of three specific aims, subdivided into 7 tasks, which were further divided into 20 subtasks. In year 1, I accomplished seven subtasks (1A, 1B, 3A, 3B, 4A, 4B, and 4C), resulting in completion of Tasks #1 and #3. In year 2, I performed subtasks 2A, 2B, 6A, 7A, and 7B, resulting in progress in Tasks #2, #6, and #7. In year 3, I was able to complete an additional three subtasks (5A, 5B, and 6B), resulting in progress in Tasks #5 and #6. In year 4, I made progress in subtasks 4D and 6C, resulting in completion of Tasks #4 and progress in Task #6. In year 5, I completed subtasks 2C and 7C, resulting in progress in Tasks #2 and #7, as described in detail below. In total, I have now completed 19 out of 20 proposed subtasks. The findings associated with these subtasks and tasks from year 5 are detailed below.

The goal of Task #2 was to assess for the effect of ERG overexpression on radiation response (+/- DNAPK inhibition). Subtask 2A was to obtain institutional approval for mouse studies, and this subtask was completed in year 2. Subtask 2B was to create bioluminescent tumor cells, and this subtask was also completed in year 2. Subtask 2C was to perform a pilot xenograft study to assess baseline rates of growth in ERG+ vs ERG- tumors and to confirm stability of ERG overexpression in these xenografts. Subtask 2D was to execute a full xenograft experiment as described in our original proposal.

While I did obtain institutional approval for the proposed animal studies (subtasks 2C and 2D) in year 2 of this proposal, I have not, to date, been able to obtain the necessary ACURO clearance from the DOD to proceed with these studies. Part of the delay, in year 3, was that I could not obtain sufficient quantities of clinical-grade drug (a DNAPK inhibitor) necessary to complete subtask 2D. Once I had obtained sufficient amounts of drug to proceed with subtask 2D, I submitted the full ACURO application in year 4 (June 2014). I was asked to provide additional information to ACURO, which I subsequently did. In my last email correspondence from ACURO, dated May 7, 2015, Joseph Kallhoff from ACURO notified me that all the necessary information for my ACURO application had been submitted, and that my proposal was awaiting review by an ACURO veterinarian. Earlier messages from ACURO informed me that increased ACURO workload was lengthening review times (for animal use applications) to several months or more, so even though I received this last correspondence 6 months ago, I am still awaiting a response from ACURO regarding whether I can proceed with my proposed animal applications.

However, during the past year, as part of a separate project NOT funded by the Department of Defense, I have been able to complete subtask 2C (a pilot xenograft study assessing baseline growth of ERG+ vs ERG- tumors and the stability of ERG overexpression in these xenografts). This non-DOD-supported project investigated the utility of PARP1 inhibition in radiosensitizing ERG+ vs ERG- tumors (and thus differed from my DOD-sponsored project to evaluate DNAPK inhibition as a strategy for radiosensitizing ERG+ vs ERG- tumors). However, the control groups for the PARP1 inhibitor project assessed for baseline levels of growth of ERG+ vs ERG- tumors – these growth rates are shown in Figure 1A below, in the groups represented by the black and red lines. In addition, I was able to confirm the stability of ERG overexpression in this xenograft model, shown in the western blots in Figure 1B below. Thus, this PARP1 inhibitor project has now generated the data necessary to complete subtask 2C of my DOD grant. I would like to reiterate that while this separate PARP1 inhibitor project has generated the data necessary to complete subtask 2C, no DOD funds were used to support the mouse project below, as I realize that, until I receive ACURO approval, I cannot use any DOD funds for any mouse projects. In addition, since this PARP1 inhibitor project was funded by a foundation that did not require further animal use approval beyond that granted by my institution, I had the necessary approval to complete the mouse studies shown in Figure 1.

Figure 1

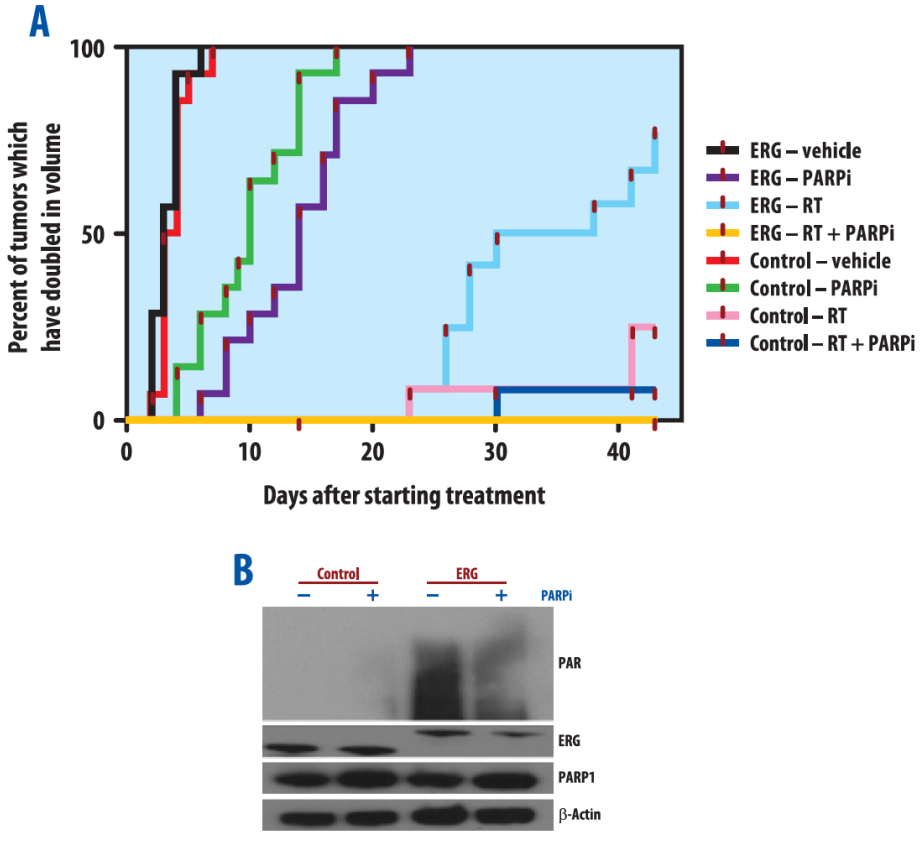

Figure 1: ERG overexpression confers radiation resistance in vivo, which is reversed with PARP inhibition. Two weeks after engraftment, PC3 ERG+ and control xenografts were treated with the PARP1 inhibitor ABT-888 (100 mg/kg twice daily) alone, radiation (RT) alone (2 Gy for 5 days), or in combination. The cumulative incidence plot depicts the percentage of tumors in each treatment group that have doubled in volume as a function of time. (A) ERG overexpression confers radiation resistance as shown by a shorter time needed for ERG+ tumors to achieve volumetric doubling than the control tumors. ERG overexpression causes sensitivity to PARP inhibition that is enhanced in combination with radiation treatment. (B) Western blot analysis of

ERG+ PC3 cell xenografts treated with or without 100 mg/kg ABT-888 for 4 hours before harvesting. Total PAR, ERG, PARP1, and actin were assessed. (Note that the control tumors harbor a truncated nonfunctional version of ERG, as opposed to full-length functional ERG in the ERG+ tumors).

As I am still awaiting a response from ACURO, I have not been able to complete subtask 4D (a full xenograft study assessing radiation +/- DNAPK inhibitor), and therefore am requesting a no-cost extension to be able to complete the study. I have established the relevant model systems and have obtained the necessary reagents to perform the study, but cannot proceed until I have a response from ACURO.

The goal of Task #7 was to determine whether ETS gene fusion status predicts for radiation resistance in prostate cancer samples from patients. Subtask 7A was to obtain institutional review board approval for a retrospective clinical review of the tissue bank patient cohort, and this was achieved in Year 2. Subtask 7B was to make sure that there was clinical data available to accompany the tissue bank cohort, and this was also achieved in Year 2. Subtask 7C was to determine whether ETS gene fusion status associated with clinical outcomes following radiation therapy, by analyzing both the collected biomarker and clinical data. However, in year 2 of this grant period, I realized that the majority of samples were exhausted from the institutional tissue bank that I had planned to analyze – they had been consumed by other investigators for other studies. In year 3 of this grant period, I developed a plan to obtain samples instead from the national RTOG cooperative group, and submitted an application to obtain RTOG tissues. This application was tentative approved by RTOG, but in year 4, I was told that I had to submit a second application to the CTEP branch of the National Cancer Institute, due to changes in rules governing RTOG tissue use. My CTEP application was subsequently rejected because CTEP is prioritizing studies that validate a known finding, instead of those seeking to first-time proof of a scientific hypothesis. Despite these hurdles, I have, in year 5, been able to complete the analysis that I proposed in Subtask 7C, using publicly available datasets.

Five years ago, when I submitted this DOD grant application, I had proposed to assess for associations between ETS fusions status and radiation response in clinical samples. My initial strategy was to achieve this goal using institutional samples, which I realized was not possible in year 2 of this application. However, in the 5 years since I began this work, large publicly available datasets have been generated, which pair high-throughput biomarker data with clinical outcomes. In fact, I have previously published several studies analyzing these publicly available datasets (Tomlins SA et al, European Urology 2015, PMID 25964175, Zhao S et al, Prostate Cancer Prostatic Diseases 2015, PMID 25986914; Prensner JR et al, Lancet Oncology 2014, PMID 25456366). Over the past year, I realized that there was sufficient data in these publicly available datasets to permit an analysis of ERG status and radiation response, and I proceed with such an analysis. This analysis, summarized in Figure 2 below, demonstrated that ETS fusion status was not associated with response to radiation, in multiple cohorts. Because this data is all publicly available (i.e., can be accessed by anyone over the internet) and is completely de-identified, this analysis did not require HRPO review. The available biomarker and clinical data from these de-identified patients is available on the NCBI Gene Expression Omnibus, with accession numbers GSE46691 and GSE62116.

Figure 2

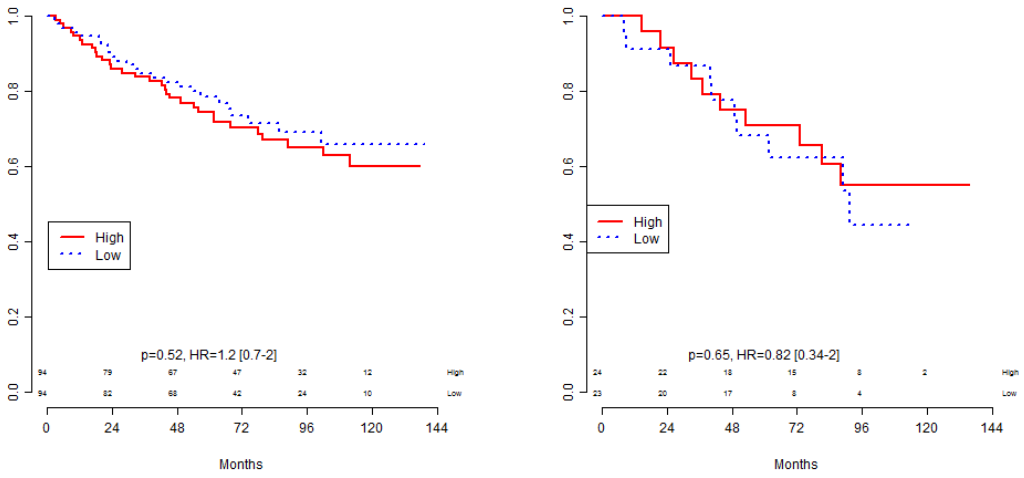

Figure 2: Two publicly available cohorts, totaling 225 prostate cancer patients treated with radiation, were analyzed for associations between ETS gene fusion status and metastatic progression ("High" denotes presence of an ERG fusion and "Low" denotes absence of an ERG fusion). ETS gene fusions status did not predict outcomes following radiation therapy, as demonstrated by Kaplan Meier analyses.

Thus, to summarize, Year 5 of my grant period is notable for completion of two subtasks, 2C and 7C. I have now completed 19 of the proposed 20 subtasks over the five years of this grant, and am awaiting a response from ACURO before proceeding with the 20th substask. Overall, the five years of this grant have been quite successful.

Research achievements: Milestones

In the original Statement of Work, 11 milestones were identified, and targeted over the 5 year course of this grant. To date, I have completed 10 out of 11 milestones (Milestones #1, #2, #4, #5, #6, #7, #8, #9, #10, and #11) during the 5 years of this proposal. I am awaiting ACURO approval for subtask 4D; completion and publication of the results from subtask 4D will allow be achieve the final milestone.

Training achievements

In my original grant application, I highlighted a series of training program activities which I hoped would contribute substantially to my scientific development. Over the past year, as proposed, I have continued to attend a number of basic science seminars, hosted by the Departments Medicine, and Molecular and Cellular Biology, which have broadened by scientific knowledge within my field. I have also regularly attended Gene Fusion and Cancer Biology Research Meetings, run by my mentor Arul Chinnaiyan, as well as the Pathology and Radiation Oncology Research Seminars, run by the two departments with which I am affiliated. Additionally, I have renewed my "Training in the Responsible Conduct of Research" certification, and presented at the national meetings noted above in the milestones section. I have presented my research at national conferences, including the *AACR* annual meeting, the *AACR Prostate Cancer* meeting, the *ASCO* meeting, the *Prostate Cancer Foundation* annual meeting, and the *ASTRO* annual meeting. Finally, I have met regularly with my mentors, Drs. Arul Chinnaiyan, Ted Lawrence, and Tom Carey, as planned in my original proposal.

Career achievements

The overall goal of my DOD Mentored Physician Research Training Award was to help me develop a career as a physician scientist committed to prostate cancer research. This grant has really helped me accomplish this goal, both directly and indirectly. Because of my need to obtain tissue specimens to fulfill Aim 3 of this grant, I approached the Radiation Therapy Oncology Group (RTOG), and began regularly attending their Genitourinary Cancer Translational Research Committee meetings. Because of my increasing involvement with this group, I was appointed as chair of this committee. As chair of this committee, my role is to help direct RTOG-based prostate cancer research on a national level. This role has resulted in national recognition, as I was asked to present my research from this DOD grant in the 2011 AACR Prostate Cancer conference and the 2012 ASTRO meeting. Similarly, I moderated one of the 3 sessions at the 2013 ASCO GU conference (my session was focused on translational research in prostate cancer), and I chaired and organized a session on localized prostate cancer at the 2015 AACR Annual Meeting. Over the past few years year, I have also served as a grant reviewer for the NIH Cancer Biomarker Study Section (four times), DOD study sections (twice), Prostate Cancer Foundation Young Investigator and Challenge grants (six times), and Prostate Cancer Canada/Movember grants (once). Additionally, my reputation as a translational prostate cancer researcher led to my nomination and subsequent election to the National Cancer Institute Genitourinary Cancer Steering Committee, which reviews national cooperative group clinical trial proposals in prostate cancer. Also, I was named as the Chair of the Biology Scientific Track for ASTRO (American Society of Radiation Oncology), the national organization for radiation oncologists – in this role, I lead and organize the biology scientific sessions for this organization. Because of these successes, my chairman appointed me as Chief of the Division of Translational Genomics in the Department of Radiation Oncology at the University of Michigan. Of note, I recently accepted a new position as Vice Chair, and Director of Translational Research, for the Department of Radiation Oncology at the University of California at San Francisco, and will be joining the UCSF faculty as an Associate Professor in July 2016.

My DOD-sponsored project has led to the preliminary data necessary for several grants that I have received over the past four years, including a Celgene Translational Award ($500,000 over 2 years) and five separate Prostate Cancer Foundation (PCF) Challenge Award ($1,000,000 split among co-Principal Investigators over 2 years). This includes two PCF Challenge Awards focused on DNA repair (entitled "*Interrogation of Aberrant DNA Repair in Sporadic Prostate Cancer"* and "*Targeting DNA Repair Pathways to Improve Treatment for Advanced Prostate Cancer"*), which stem directly from the findings in this DOD grant and seek to translate some of these findings into the clinic. The other three PCF Challenge grants, which include a genomic sequencing study to identify biomarkers of radioresistance and two additional studies seeking to develop targeted therapies for prostate cancer, build upon skill sets that I have developed in the course of completing the subtasks and training program specified in this DOD grant. In addition, I was funded for five additional prostate cancer-based grants. One of these grants, from the Fund for Cancer Research ($75,000 for 1 year), was based directly on extending the work initiated in Aim 1 of this DOD PCRP grant. Two of the other four grants (I am co-PI of project within a NIH SPORE grant, entitled "Development of Novel BET Bromodomain Inhibitors for the Treatment of Advanced Prostate Cancer" and am a key co-investigator of a U10 grant entitled "*Integrated Translational Genoproteomics Center at Washington University"*) are NIH grants. The other two grants (Mazzone grant and Medivation/Astellas Investigator Grant) are not directly related to the work included in this DOD PCRP grant, but do focus on different aspects of prostate cancer. In total, during the five years of this DOD PCRP grant, I have received In addition, over the past year, I have received 10 additional grants, from both NIH and Foundation sources. Much of this success has been based upon the data generated and experienced gained from this DOD Grant. In addition, I have had six manuscripts accepted for publication,

and a seventh one in submission, based on work from this proposal (detailed in the reportable outcomes section below). In addition to these 7 manuscripts (see references 1-7 below), I have published 97 additional manuscripts over the five years of this grant, including approximately 25 from the last year. I would like to thank the DOD for making all of this possible for me.

Key Research Accomplishments:
The key research accomplishments from the past year of this grant proposal include the following:

- Determination of baseline levels of growth in ERG+ vs ERG- xenografts
- Discovery that, in clinical samples, ERG fusion status does not predict for radiation response (which differs from data generated from preclinical models in this grant)

These accomplishments add to the findings from the first four years of the grant proposal, which showed that:

- ERG overexpression in prostate cancer cell lines confers radiation resistance
- This ERG-associated radiation resistance is mediated by increased efficiency of DNA repair in response to radiation
- ERG interacts with the repair protein DNAPK in a DNA-independent manner, at its tyrosine 373 site
- DNAPK knockdown or inhibition preferentially radiosensitizes ERG-positive vs ERG-negative cells, and can reverse ERG-mediated radiation resistance
- ERG is diffusely localized through the prostate cancer cell and does not redistribute upon genotoxic stress
- ERG-mediated invasion depends on the ETS subdomain of the ERG protein
- ERG FISH can be optimized in old formalin-fixed paraffin embedded tissue

Reportable Outcomes:
The past year of work from this grant proposal has resulted in the following reportable outcomes:

1) A highlight of my work on the DOD CDMRP website (http://cdmrp.army.mil/pcrp/research_highlights/15feng_highlight.shtml)
2) A manuscript, following from Aim 2 of this grant, accepted at *Cancer Cell* (on which I am co-senior author)[1]
3) A manuscript, relating to Aim 3 of this grant, accepted at *European Urology* (on which I am senior author)[2]
4) Visiting Professorships at the Cleveland Clinic, UT Southwestern, UCSF, UCLA, and Harvard

These outcomes add to the following reportable outcomes from the four years of the grant:

5) A manuscript, reviewing data from Aim 1 this grant, published in *Clinical Cancer Research*[13] (on which I am first author)
6) A funded Challenge grant from the Prostate Cancer Foundation, entitled "*Targeting DNA Repair Pathways to Improve Treatment for Advanced Prostate Cancer"*
7) Publication of work from Task #4 in a *Cancer Cell* manuscript[4], co-published with my mentor and primary collaborator, Dr. Arul Chinnaiyan
8) Two publications on ETS gene fusions in prostate cancer, published in the journal *Curr Drug Targets*[5] and *Neoplasia*[6]
9) A publication on DNAPK in prostate cancer, published in the journal *Cancer Discovery*[7]
10) Oral presentation on work from Task #4, at the 2010 American Society of Therapeutic Radiology and Oncology Annual Meeting[8]
11) Poster discussion presenting work from Tasks #1 and #3, at the 2011 American Society of Clinical Oncology Annual Meeting[9]
12) Invited oral presentation on work from Tasks #1 and #3, at the 2011 Prostate Cancer Foundation Annual Meeting
13) A funded Young Investigator Award from the Prostate Cancer Foundation ($225,000 over 3 years), entitled "*Cooperativity between TMPRSS2:ERG Gene Fusions and PTEN*

Genomic Deletions in the Radiation Resistance of Prostate Cancer", from January 2011 to January 2014

14) Oral presentation of work from this grant proposal, at the 2012 AACR Prostate Cancer Conference
15) An invited presentation, in which I reviewed data from this grant, at the Winship Cancer Center (at Emory)
16) A funded Challenge Grant from the Prostate Cancer Foundation ($1,000,000 over 3 years, split among 4 co-principal investigators, of which I am one), entitled "*Interrogating DNA repair aberrations in advanced prostate cancer*", from 8/2012-7/2015
17) A funded Translational Award from the pharmaceutical company Celgene ($500,000 over 2 years, on which I am PI), entitled "CC115 as a therapeutic approach for metastatic Ewing's sarcoma or prostate cancer", from 4/2012-4/2014
18) A funded grant from the Fund For Cancer Research, entitled "Investigating ETS Gene Fusions as Predictive Biomarkers of Radiation Resistance and Targets for Radiosensitization" ($75,000 over 1 year)

Conclusion:

This Annual Report summarizes the five-year accomplishments associated with the Department of Defense Physician Research Training Award (W81XWH-10-1-0582), awarded to Felix Feng, M.D. Overall, the fifth year of this grant period has been successful, and has resulted in two manuscripts (*Cancer Cell* and *European Urology)* and highlighting of this research on the DOD PCRP website. My research also resulted in invitations to 5 visiting professorships this year. In total, this grant has resulted in five subsequent funded grants, seven publications, five presentations, five visiting professorships, and several national leadership positions. In addition, I have completed 19 out of the 20 subtasks proposed for this 5-year grant. Additionally, I have met the training achievements specified in my original grant.

I have submitted an application for a no-cost extension, to allow me to complete the 20th subtask proposed for this grant. In order to complete this last subtask, I need to perform xenograft studies, but have been awaiting ACURO approval for over 6 months. The no-cost extension would hopefully allow the necessary time to obtain ACURO approval so that I can complete my proposed studies.

The research proposed in this training grant represents an important area within the field of prostate cancer research. Because ETS gene fusions are thought to be driver alterations in over half of all prostate cancers, understanding the mechanistic and potential clinical implications of these gene fusions has significant ramifications, particularly in the context of radiation therapy, which represents one of the primary treatment modalities for localized prostate cancer. Our findings are that ERG fusions can promote oncogenic phenotypes through their association with DNA-PK. These findings suggest that DNA-PK inhibition should be explored as a clinical strategy for radiosensitizing ERG+ prostate cancers.

I would like to thank the DOD review committee for providing me this grant to accomplish the proposed research.

References:

1) Goodwin JF, Kothari V, Drake JM, Zhao S, Dylgjeri E, Dean JL, Schiewer MJ, McNair C, Magee MS, Den RB, Zhu Z, Graham NA, Vashisht AA, Wohlschlegel JA, Graeber TG, Davicioni E, Karnes RJ, Tomlins SA, Sharifi N, Witte ON, Feng FY** and Knudsen KE**. DNA-PK mediated transcriptional regulation drives tumor progression and metastasis. *Cancer Cell* 2015, 28(1): 97-113. **indicates equal senior authorship
2) Tomlins SA, Alshalaifa M, Davicioni E, Erho N, Yousefi K, Zhao S, Haddad Z, Den RB, Dicker AP, Trock BJ, DeMarzo AM, Ross AE, Schaeffer EM, Klein EA, Magi-Galluzzi C, Karnes RJ, Jenkins RB, and Feng FY. Characterization of 1577 primary prostate cancers reveals novel biological and clinicopathologic insights into molecular subtypes. *European Urology* 2015; 68(4): 555-67.
3) Feng FY, Brenner JC, Hussain M, Chinnaiyan AM. Molecular Pathways: Targeting ETS Gene Fusions in Cancer. *Clin Cancer Res*. 2014 Sep 1;20(17):4442-8.
4) Brenner JC, Ateeq B, Li Y, et al: Mechanistic rationale for inhibition of poly(ADP-ribose) polymerase in ETS gene fusion-positive prostate cancer. *Cancer Cell* 19:664-78, 2011
5) White NM, Feng FY, Maher CA. Recurrent rearrangements in prostate cancer: causes and therapeutic potential. *Curr Drug Targets*. 14(4):450-9, 2013.
6) Han S, Brenner JC, Sabolch A, Jackson W, Speers C, Wilder-Romans K, Knudsen KE, Lawrence TS, Chinnaiyan AM, **Feng FY**. Targeted Radiosensitization of ETS Fusion-Positive Prostate Cancer through PARP1 Inhibition. *Neoplasia* 2013 Oct; 15(10): 1207-17.
7) Goodwin JF, Schiewer M, Dean JL, Schrecengost RS, Han S, Den RB, Dicker AP, Feng FY, and Knudsen KE. A hormone-DNA repair circuit governs the response to genotoxic insult. *Cancer D*iscov. 2013 Nov;3(11):1254-71.
8) Feng FY, Han S, Brenner C, et al: PARP inhibition reverses radiation resistance conferred by ETS fusions in prostate cancer. *J Clin Oncol* 29:4545, 2011

Appendices:

None